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Review Article

A Review: Determination of Itopride Hydrochloride in biological fluid and Pharmaceutical Dosage Forms

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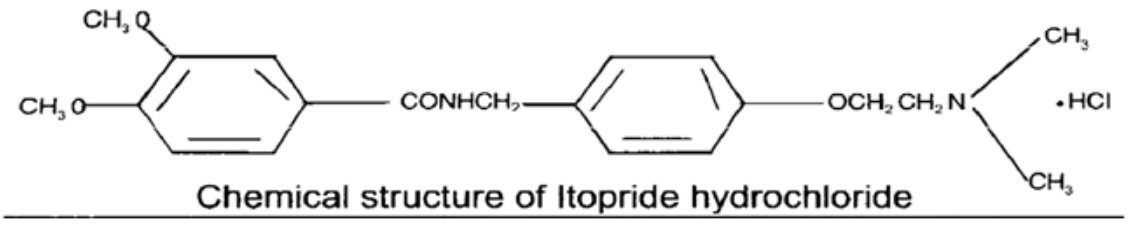
ABSTRACT

Itopride Hydrochloride is a novel, synthesized, gastro prokinetic drug, which stimulates gastrointestinal motor activity through the synergistic effects of dopamine D2-receptor blockade and acetylcholine esterase inhibitors. Chemically, it is N-[[4-[2-(Dimethyl amino) ethoxy] phenyl] methyl]-3, 4-dimethoxy benzamide hydrochloride. Benzamide structure, amide and ether linkages in the drug molecule make it susceptible to degradation. Thus a prokinetic drug like Itopride Hydrochloride by virtue of its efficacy and tolerability could be considered as a drug of first choice and a welcome addition to the drug armamentarium for the symptomatic treatment of NUD (non-ulcer Dyspepsia) and other gastric motility disorders including functional bowel disorders. This review consists of various analytical methods for determination of Itopride Hydrochloride in various marketed pharmaceutical preparation and in biological fluids. Analytical method consists of various spectroscopic methods, chromatographic methods and other methods.

Keywords: Itopride Hydrochloride, Chromatographic Methods, Compendial Methods, UV Spectroscopic

INTRODUCTION[1-6]

STRUCTURAL FORMULA:



Chemical structure of Itopride hydrochloride

MOLECULAR FORMULA: $C_{20}H_{26}N_2O_4HCL$
MOLECULAR WEIGHT: 394.93 g/mol
CHEMICAL NAME:
N-[[4-[2-(Dimethyl amino) ethoxy] phenyl] methyl]-3, 4-dimethoxy benzamide hydrochloride.
CATEGORY: Anticholinesterase

DOSE:150 mg daily
DESCRIPTION: white amorphous powder
SOLUBILITY:
Soluble in methanol, water, dimethyl sulphoxide, N, N-dimethyl formemide.
Springily soluble in ethanol, propyleneglycol,

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PHARMATUTOR
PHARMACY INFOPEDIA
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polyethylene glycol. **Very slightly soluble** in hexane, dichloromethane, methyl benzene.

PHARMACOLOGICAL ACTION

Itopride has anticholinesterase (AchE) activity as well as dopamine D2 receptor antagonistic activity and is being used for the symptomatic treatment of various gastrointestinal motility disorders. It is well established that M3 receptors exist on the smooth muscle layer throughout the gut and acetylcholine (ACh) released from enteric nerve endings stimulates the contraction of smooth muscle through M3 receptors. The enzyme AChE hydrolyses the released ACh, inactivates it and thus inhibits the gastric motility leading to various digestive disorders. Besides ACh, dopamine is present in significant amounts in the gastrointestinal tract and has several inhibitory effects on gastrointestinal motility, including reduction of lower esophageal sphincter and intragastric pressure. These effects appear to result from suppression of ACh release from the my enteric motor neurons and are mediated by the D2 subtype of dopamine receptors. Itopride, by virtue of its dopamine D2 receptor antagonism, removes the inhibitory effects on Ach release. It also inhibits the enzyme AchE which prevents the degradation of Ach.

The net effect is an increase in ACh concentration, which in turn, promotes gastric motility, increases the lower esophageal sphincter pressure, accelerates gastric emptying and improves gastro-duodenal coordination (Figure)

This dual mode of action of Itopride is unique and different from the actions of other prokinetic agents available in the market.

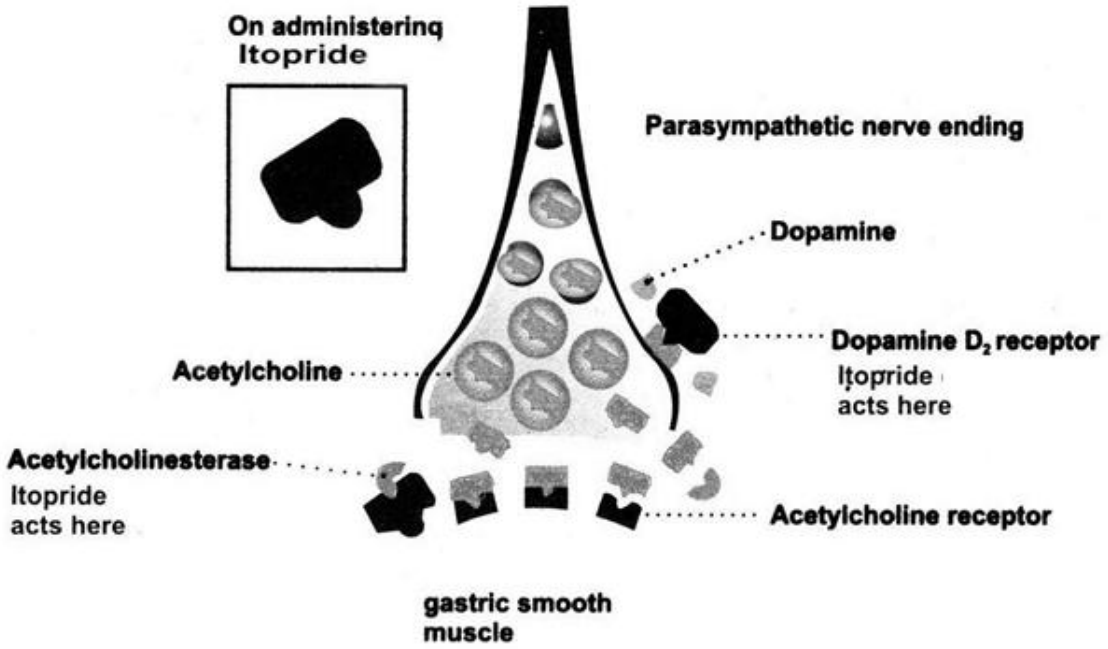

Figure: Mode of action of Itopride.[4]

PHARMACOKINETICS

On oral administration, Itopride is rapidly and extensively absorbed and peak serum concentrations are achieved within 35 minutes after oral dosing. Thus it has a rapid onset of action, unlike cisapride and mosapride, which

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take around 60 minutes to reach peak plasma concentrations. Itopride is metabolized in the liver by N-oxidation to inactive metabolites by the enzyme flavin-containing monooxygenase (FMO). The half-life of Itopride is about 6 hours. It is excreted mainly by the kidneys as metabolites and unchanged drug.

SIDE EFFECTS

Rash, diarrhea, giddiness, exhaustion, back and chest pain, increased salivation, constipation, abdominal pain, headache, sleeping disorder, dizziness, galactorrhea and gynecomastia.

ANALYTICAL METHODS

This all are the methods which are used for the determination of Itopride Hydrochloride in marketed formulation and in biological fluids. This all analytical methods are reported which are seen during the literature survey. This article describes the review on the all reported analytical methods with specific conditions.

I.COMPENDIAL METHODS:

Itopride Hydrochloride is not official in any pharmacopeia.

II. CHROMATOGRAPHIC METHODS:[7-14]

Various chromatographic methods are used for the determination of the Itopride Hydrochloride alone or combination with other drugs in various marketed formulation and in biological fluids like human plasma and urine. Chromatographic methods like High performance liquid chromatography (**HPLC/RP-HPLC**), High performance thin layer chromatography (**HPTLC**) with UV detection or with flourometric detection are used. In which the stationary phase commonly used is **C18 column** and commonly used wavelength for detection is 258nm.Mobile phase is varies with condition of method in various proportion. Below in table describes the summary of the various chromatographic methods are used with the method description.

Table No.1: Summary of Chromatographic Methods of Itopride hydrochloride

Title	Method	Mobile Phase	Stationary Phase	Wavelength (nm)
Determination of Itopride Hydrochloride in capsule formulation[07]	HPLC	Methanol-Water-Triehanolamine-Glacial ascetic acid (with the proportion of 40:60:0.5:0.3,v/v/v/v)	C18 column (4.6mm×250mm)	258
Optimized method for the determination of itopride in human plasma[08]	HPLC with flourometric detection	Acetonitrile-Triethylamine-dihydrogen potassium phosphate (14.5:0.5:85,v/v/v)	octadecylsilica column (55 mm × 4 mm, 3 µm particles),	250/342
Chromatographic determination of Itopride Hydrochloride in the presence of its degradation products[09]	HPLC	Methanol-Water(70:30,v/v)	Kromasil column [C_{18} (5-µm, 25 cm×4.6 mm, ID)]	258
Simultaneous	RP-HPLC	Acetonitrile: buffer	Luna C18 (5µ M,	

PHARMATUTOR
PHARMACY INFOPEDIA
ISSN: 2347-7881

determination of Rabeprazole sodium and Itopride Hydrochloride in solid dosage form[10]		(35:65 v/v)	25 cm×4.6 mm i.d) phenomenex	266
Simultaneous determination of Esemoprazole and itopride in capsule[11]	RP-HPLC	Buffer(Ammonium Acetate,pH-5.5):Water: Methanol (25: 15: 60,v/v/v)	Phenomenex C18	275
Determination of Itopride Hydrochloride in its pharmaceutical preparation and in bulk drug[12]	HPTLC	Methanol-Ethyl acetate-Toluene-Triethylamine (1.0: 2.5: 6.0: 0.5,v/v/v/v)	Silica gel 60F 254 TLC plates	230
Simultaneous determination of Rabeprazole sodium and Itopride Hydrochloride in solid dosage form[13]	HPTLC	n-butanol: toluene: ammonia (8.5:0.5:1 v/v/v)	precoated silica gel G60F254 plate (10×10 cm)	288
Stability indicating high performance thin-layer chromatographic method for simultaneous estimation of pantoprazole sodium and itopride hydrochloride in combined dosage form[14]	HPTLC	Methanol: Water: Ammonium acetate; 4.0:1.0:0.5 (v/v/v)	Aluminium plates precoated with silica gel 60F254	289

II. UV SPECTROSCOPIC METHOD:[15-19]

A simple, precise and economical spectrophotometric method for the estimation of Itopride Hydrochloride in pharmaceutical bulk and tablet dosage form was developed and validated. Identification was carried out using a UV- visible double beam spectrophotometer detector with working wavelength at 258nm in water and methanol medium. The method was validated with respect to its specificity, linearity range, accuracy and precision in analytical media. Itopride Hydrochloride show the maximum absorbance (λmax) at 258 nm. Simple UV spectroscopy, first derivative spectroscopy, AUC method and absorption ratio methods are reported for determination of the Itopride Hydrochloride in marketed formulation. Below in table describes the various chromatographic methods with the method description and condition which are reported on review literature.

PHARMATUTOR
PHARMACY INFOPEDIA
ISSN: 2347-7881

Table No.2: Summary of UV spectroscopic methods of Itopride Hydrochloride

Title	Method	Medium	λmax (nm)	R^2
Spectrophotometric method development and validation of Itopride Hydrochloride in bulk and dosage form[15]	Simple uv spectroscopy method	0.1N HCL	258	0.999
Estimation of Itopride Hydrochloride in Pharmaceutical Formulation[16]	Simple uv spectroscopy method	Distilled water	258	0.9999
	First derivative method	Distilled water	247	0.9998
	AUC method	Distilled water	262-254	0.9999
Estimation of Itopride Hydrochloride from tablets formulations using Methyl orange reagent[17]	New Visible Spectrophotometric method	Distilled water	418.5	0.9991
Simultaneous estimation of Rabeprazole sodium and Itopride Hydrochloride[18]	Q-value method	Methanol	284&266.4	0.9991& 0.9999
	Simultaneous equation method		284&258	0.9992& 0.9991
Simultaneous estimation of Pantoprazole sodium and Itopride Hydrochloride[19]	First order derivative UV spectrophotometry	Distilled water	238.5& 288	0.9991& 0.9992

III.MISCELLANOUS METHODS:[18-21]

Most widely used methods are mainly HPLC, UV and HPTLC for determination of Itopride Hydrochloride in various formulation or in biological fluids but along with that other methods are also used which are seen during the literature survey. The summary of that methods are described below in table.

Table No.3: Summary of Miscellaneous methods of Itopride Hydrochloride

Sr.No.	Title	Method
1	Stability-Indicating Spectrofluorimetric Method for Determination of Itopride Hydrochloride in Raw Material and Pharmaceutical Formulations[20]	Spectrofluorimetric method
2	Identification of Forced Degradation Products of Itopride by LC-PDA and LC-MS[21]	LC-PDA & LC-MS
3	Determination of itopride in human plasma by liquid chromatography coupled to tandem mass spectrometric detection: Application to a bioequivalence study[22]	LC-MS/MS
4	Simultaneous estimation of Itopride Hydrochloride and Domperidone in human plasma[23]	LC-MS

PHARMATUTOR
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CONCLUSION

The presented review highlights on various analytical methods reported on Itopride Hydrochloride and in combination with other drug. HPLC-HPTLC-UV methods were found to be most widely used. Various chromatographic conditions are presented in under Table. The faster time, high sensitivity; specificity and better separation efficiency enable HPLC to be used frequently for the determination of Itopride Hydrochloride in the comparison with the other methods. There is no doubt on the fact that these chromatographic methods are rapid and far more economical. Other methods are also useful. In this way various analytical methods for the estimation of Itopride Hydrochloride in bulk or in various matrixes like plasma, alone or in combination with other drugs is discussed. The presented information is useful for the researchers especially those involved in the formulation development and quality control of Itopride Hydrochloride in combination with other drug.

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